

II. REMARKS

Claims **56, 57, 59-67, 69, 70, 73-79** and **86-89** are pending in the subject application, were examined and stand variously rejected. By this amendment and response, claim **90** has been added and claims **67, 86, 87** and **89** have been canceled without prejudice or disclaimer. Applicants respectfully reserve the right to file on or more continuation applications related to the same subject matter as the canceled claims.

Claims **56, 57, 62-66, 76, 77, and 88** were amended. Support for claim **90** is found specifically at paragraphs [0187] to [0190] of the specification.

Many of the claims were amended to correct grammatical errors. The other amendments are supported in the specification. For example, support for the amendments to claims **56 and 57** is found in the application papers on page 34, lines 10 to 28. Support for claim **90** is specifically located on page 34, lines 2-4 and 11-14. No new matter has been added by these amendments. Accordingly, entry thereof is respectfully requested.

In view of the preceding amendments and the remarks which follow, reconsideration and withdrawal of the rejections is respectfully requested.

Claim Informalities

Claims **62** and **63** stand objected to for alleged informalities such as typographical errors and missing punctuation. The claims have been amended in a sincere effort to remove the grounds for rejection. Claim **57** has also been amended to correct a grammatical error. Reconsideration and withdrawal of the objections is respectfully requested.

35 U.S.C. § 101

Claims **56** and **57** stand rejected under 35 U.S.C. § 101 as allegedly granting to a patent holder an impermissible ownership right under the 13th Amendment to the United States Constitution's prohibition against involuntary servitude. The claims in question had recited "metabolites thereof formed after administration to a subject".

Applicants respectfully traverse. The claims recited specific metabolites that are known to be formed in vivo, but synthesized ex vivo and administered to the patient. However, without conceding the correctness of the Office's position and merely to advance prosecution of the application, the claims have been amended to remove this language thus rendering the rejection moot. Withdrawal of the rejection is respectfully requested.

35 U.S.C. § 112, First Paragraph

Claims **56, 57, 59-67, 69, 73-79 and 86-89**, maintained the rejections under 35 U.S.C. § 112, first paragraph for the reasons of record.

With respect to the compounds of claim **62**, the Office alleged that they are directed to a vast number of chemical species that have not been described in the specification to enable the practitioner to make and use the same. The Office objected to the definition of substituents allegedly because the specification only supplies a limited number of examples.

Applicants respectfully traverse. The fact that the number of species encompassed is large as compared to the working examples in a specification is not, by itself, an adequate basis for rejection under 35 U.S.C. § 112, first paragraph. Applicants have not been provided technically specific statements of fact to which they can reply. For example, claim **62** presents two variables, the substituent of R1 and Q, and Q being limited to 5 specific structures with minor modifications. Which of the embodiments for R1 are beyond the scope of the specification? Which of the

embodiments for Q (other than the phosphoramidate embodiment for R7 which is addressed) are beyond the scope of the specification, especially viewed in combination with the wealth of prior art, that Applicants have to the best of their ability, brought to the attention of the Patent Office? After the Office has provided a reasoned statement that specifically points out the alleged failures of the specification, Applicants can provide format a concise and cogent reply. At this point Applicants would be guessing as to the technical basis for the rejections.

The Office also objected to claim **62** on the ground that “derivatives or analogues” in claim **62** is overly broad since structures are not provided. Applicants respectfully traverse. Without conceding the correctness of the Office’s rejection, claim **62** has been amended to remove the term “analogues” and now recites only specific derivatives, i.e., those which are either “phosphoryl derivatives” or phosphoramidatyl derivatives of a naturally occurring amino acid”. The term “derivative” is defined in Applicants’ specification and is a term well known to those of skill in the art. Two specific phosphoramidatyl derivatives of naturally occurring amino acids are provided in the specification, leaving 18 possible derivatives remaining (there being 20 naturally occurring amino acids). Methods for the synthesis of other aminocyl phosphoramidate derivatives are well known in the art and utilize techniques in common to all amino acids due to the functional groups in common between all α -amino acids. The Examiner is referred to Miao et al, “A stepwise one pot synthesis of alkyl thiophosphoramidate derivatives of nucleosides,” Syn. Comm. (2002) 32:1159-1167 and PCT publication WO 2005/012327, page 19, lines 24-31 for methods applied in general to the synthesis of nucleoside phosphoramidates. The references are provided as addenda to this paper for the Examiner’s convenience. Applicants therefore request that the grounds for rejection be withdrawn.

The Examiner also objected to the terms “stereoiosomeric, enantiomeric and anomeric” in claim **62** on the ground that not all forms have been synthesized or that any reasonable predictive proportion of same have been tested to determine that the

claimed pharmaceutical activity occurs in some subset thereof.

Applicants respectfully traverse. Without conceding the correctness of the Office's position and merely to advance prosecution and allowance of this application, the claim has been amended.

The Examiner also stated with respect to method claims **56, 57 and 86-88**, the specification does not support the treatment of all diseases encompassed by the term cancer, autoimmune disorder and inflammatory conditions.

Applicants respectfully traverse. Applicants claims are not directed to the treatment of all cancers, autoimmune disorders and inflammatory conditions. Correlation of increased levels of expression of thymidylate synthase genes in cancer cells is well known and has been exploited for development of treatment modalities. See for example Costi, "Thymidylate synthase inhibition: a structure-based rationale for drug design," Med. Res. Rev. (1998) 18:21-42. Applicants' methods are directed only to those cells which overexpress thymidylate synthase, regardless of the type of cell. Colon cancer is only one such cancer cell. Thymidylate synthase expression levels have also been correlated with metastatic melanoma, for example. (Vlaykova et al., Oncology (1997) 54:146-152). Without acquiescing to the correctness of the Examiner's position and solely to advance prosecution applicants have amended claim 88 to incorporate the elements of claim 89 reciting that the methods of claims 56 and 57 are applied to colorectal cancer cells and breast cancer cells. Support for the amendment can be found throughout the specification.

Moreover, Applicants' specification shows how to administer the compounds and the efficacy of the compounds. Whether one or other pathology is amenable to treatment by Applicants' methods can be determined by one of skill in the art, as expressed in Applicants' specification or alternatively, by published methods, for example those disclosed in US Patent Publication No.: US 2002/0039990 A1. Withdrawal of the rejection is therefore respectfully requested.

35 U.S.C. § 112, Second Paragraph

Claims **56-57, 59-61 and 88** stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

With respect to claims **56 and 57**, the Examiner objected to use of the term “or a metabolite thereof formed after administration to the subject” because the particular structure is not defined. Applicants have amended claims **56 and 57** in a sincere effort to overcome the grounds for rejection.

The Office also objected to the use of the term “pathology characterized by hyperproliferative neoplastic cells” in claims **56 and 57** on the ground it is vague and indefinite. Applicants respectfully traverse on the ground that the claimed method is directed only to those various cells that overexpress thymidylate synthase, which has been linked to particular pathologies, without regard to specific cell type. Therefore, the claims are not as broad as the Examiner suggests. Removal of this ground for rejection is respectfully requested.

Claim **62** stands rejected for the reasons of record and to clarify the recitation of D- and L- (dextrorotatory and levorotatory) forms as stereoisomeric forms. Applicants have amended the claim to overcome the stated grounds for rejection. Withdrawal of the rejection is respectfully requested.

Double Patenting Rejections

The Office cited numerous grounds why the pending claims are unpatentable over Applicants' co-pending applications. Applicants respectfully defer responding to all double patenting rejections until allowable subject matter has been indicated by the Office in the subject application.

III. CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.


The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by the credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

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